NATIONAL GUIDELINE CLEARINGHOUSE™ (NGC) GUIDELINE SYNTHESIS

ASSESSMENT AND DIAGNOSIS OF ALZHEIMER'S DISEASE AND RELATED DEMENTIAS

Guidelines

1. **European Federation of Neurologic Studies (EFNS)**. Recommendations for the diagnosis and management of Alzheimer's disease and other disorders associated with dementia: EFNS guideline. Eur J Neurol 2007 Jan;14(1):e1-26. [253 references]
2. **Scottish Intercollegiate Guidelines Network (SIGN)**. Management of patients with dementia. A national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2006 Feb. 53 p. (SIGN publication; no. 86). [183 references]

INTRODUCTION

A direct comparison of the European Federation of Neurologic Studies (EFNS) and Scottish Intercollegiate Guidelines Network (SIGN) recommendations for the assessment and diagnosis of Alzheimer's disease (AD) and related dementias is provided in the tables below.

- Table 1 provides a quick-view glance at the primary interventions considered by each group.
- Table 2 provides a comparison of the overall scope of both guidelines.
- Table 3 provides a more detailed comparison of recommendations offered by each group for the topics under consideration in this synthesis, including:
  - History Taking and Diagnostic Criteria
  - Assessment
  - Neuroimaging
  - CSF and EEG Investigations
  - Other Investigations
- Table 4 lists the potential benefits and harms associated with the implementation of each guideline as stated in the original guidelines.
- Table 5 presents the rating schemes used to rate the level of evidence and/or the strength of the recommendations.

Following the content comparison tables, the areas of agreement and areas of difference among the guidelines are identified.

Abbreviations

- ACE, Addenbrooke's Cognitive Examination
- AD, Alzheimer's disease
- ADL, activities of daily living
- CJD, Creutzfeldt-Jakob disease
- CSF, cerebrospinal fluid
- CT, computed tomography
- DAT, dementia of the Alzheimer's type
- DLB, dementia with Lewy bodies
- DSM-IIIR, Diagnostic and Statistical Manual, 3rd edition, revised
- DSM-IV, Diagnostic and Statistical Manual, 4th edition
- EFNS, European Federation of Neurologic Studies
- EEG, electroencephalography
- FTD, frontotemporal dementia
- IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly
- MMSE, Mini-Mental State Examination
- MRI, magnetic resonance imaging
- NINCDS-ADRDA, National Institute of Neurologic, Communicative Disorders and Stroke—Alzheimer's Disease and Related Disorders Association
- NINDS-AIRENS, National Institute of Neurological Disorders and Stroke—Association Internationale pour la Recherche et l'Enseignement en Neurosciences
- PET, positron emission tomography
- PSP, progressive supranuclear palsy
- SIGN, Scottish Intercollegiate Guidelines Network
- SPECT, single photon emission computed tomography
- VAD, vascular dementia

TABLE 1: COMPARISON OF INTERVENTIONS AND PRACTICES CONSIDERED
("✓" indicates topic is addressed)

	EFNS (2007)	SIGN (2006)
History Taking and Diagnostic Criteria	✓	✓
Assessment	✓	✓
Neuroimaging	✓	✓
CSF and EEG Investigations	✓	✓
Other Investigations	✓	

TABLE 2: COMPARISON OF SCOPE AND CONTENT	
Objective And Scope	
EFNS (2007)	To present a peer-reviewed evidence-based statement for the guidance of practice for clinical neurologists, geriatricians, psychiatrists, and other specialist physicians responsible for the care of patients with dementia
SIGN (2006)	• To present evidence-based recommendations for the management of dementia • To consider investigations and interventions in which direct benefit to the patient can be demonstrated
Target Population	
EFNS (2007)	Patients with suspected or diagnosed Alzheimer's disease or other dementia disorders
SIGN (2006)	Patients with all stages of dementia excluding mild cognitive impairment
Intended Users	
EFNS (2007)	Physicians
SIGN (2006)	Advanced Practice Nurses Nurses Occupational Therapists Physical Therapists Physician Assistants Physicians Psychologists/Non-physician Behavioral Health Clinicians

TABLE 3: COMPARISON OF RECOMMENDATIONS	
History Taking and Diagnostic Criteria	
EFNS (2007)	**Clinical Diagnosis** With the remarkable exception of autosomal dominant causes of dementia, there is no specific biological marker for degenerative dementias. Therefore, in the absence of neuropathological confirmation, the aetiological diagnosis of a dementia syndrome can

	only be made in terms of probability. The clinical diagnosis should rely on criteria that have been proposed to increase the reliability and accuracy of the diagnosis. The accuracy of these diagnostic criteria varies as a function of the dementia. For AD, both the DSM-IIIR and the NINCDS-ADRDA criteria achieved a good sensitivity (up to 100%, average 81% across studies), but a low specificity (average across studies 70%) for "probable" AD, based on class I-II studies with post-mortem confirmation. For DLB, the Consortium for DLB diagnostic criteria from 1996 showed rather low sensitivities in class I and II studies. For FTD advances in the understanding of the underlying pathophysiology and genetic mechanisms have indicated that the clinical syndromes are associated with several different neuropathological abnormalities, although generally, specific sets of pathological findings have not been associated with specific clinical syndromes. For VAD, the NINDS-AIREN diagnostic criteria achieved a low sensitivity (43%), but a good specificity (95%) in the only published class I study. Mixed pathologies and the prevalent findings of vascular lesions in all patients with dementia add to the complexity of the diagnosis of VAD. **Medical History** The history should include the cognitive domains affected, the mode of onset, the pattern of progression and the impact on ADL. Past medical history, current co-morbidities, family history and educational history are important. Due both to the presence of cognitive deficit and to the possibility of anosognosia it is important to obtain a history from an independent informant. Several class I to II studies have confirmed the value of informant based instruments, such as the IQCODE and the Blessed Roth Dementia Scale (BRDS) in the detection of dementia. The clinical history should be supplemented by an independent informant where available (**Level A**).
SIGN (2006)	**History Taking and Differential Diagnosis** A detailed history is an important part of the assessment of someone with suspected dementia. Attention should be paid to mode of onset, course of progression, pattern of cognitive impairment and presence of non-cognitive symptoms such as behavioural disturbance, hallucinations and delusions. Sufficient information should be gathered to apply the diagnostic criteria discussed in this section, as a person with dementia may not be able to give a fully accurate history a relative or carer should also be interviewed. Subjective memory complaints, especially in well educated people, should be taken seriously, as these have been shown to be predictive of dementia, although they are also associated with depression and anxiety.

	There is a body of evidence showing that diagnostic criteria for probable AD, such as those based on definitions contained in the DSM-IV (see Annex 1 in the original guideline document for DSM-IV criteria) or the NINCDS-ADRDA criteria; (see Annex 2 in the original guideline document) have reasonably good diagnostic accuracy with a sensitivity of up to 80%. There have been fewer studies examining the diagnostic accuracy of criteria for VaD than for AD. In addition, VaD is not a homogenous entity, and it may be common for patients to present with both Alzheimer's and vascular pathology. None of the current diagnostic criteria perform well for mixed presentations. There is evidence to suggest that the Hachinski Ischaemic Score can be used to discriminate AD from VaD (see Annex 3 in the original guideline document) and that the NINDS-AIRENS criteria (see Annex 4 in the original guideline document) may be useful. The clinical criteria for DLB (Consortium for DLB criteria; see Annex 5 in the original guideline document) and FTD (Lund-Manchester criteria; see Annex 6 in the original guideline document) are not closely associated with neuropathological diagnoses but can still provide useful differentiating clinical features. **B** - DSM-IV or NINCDS-ADRDA criteria should be used for the diagnosis of AD. **B** - The Hachinski Ischaemic Scale or NINDS-AIRENS criteria may be used to assist in the diagnosis of vascular dementia. **C** - Diagnostic criteria for DLB and FTD should be considered in clinical assessment.
Assessment	
EFNS (2007)	**Neurological and Physical Examination** A general neurological and physical examination should be performed on all patients presenting with dementia (**Good Practice Point**). **Assessment of Cognitive Functions** An evaluation of cognitive function by a physician and/or by a clinical neuropsychologist is required for the management of patients with a prodromal, mild or moderate stage of dementia, whereas it is less essential for severely demented patients. The battery should investigate the following domains:

Global Cognitive Functions

The MMSE of Folstein et al., may help for the detection of cognitive impairment (I) and its sensitivity increases, if a decline of the score overtime is taken into account. The 7-Minute Screen and the Clinical Dementia Rating (CDR) (score = 1) demonstrate a specificity of 96% and 94% with sensitivity of 92% for the diagnosis of dementia (IV) and can be useful for the detection of dementia. These two tests can be used as screening instruments for assessing general intellectual functioning. The Mattis Dementia Rating Scale takes longer time and tests in addition several areas related to executive functions. It is, therefore, more appropriate for the assessment and follow up of FTD and fronto-subcortical dementias.

Memory Function

Memory has to be systematically assessed. Episodic long-term memory impairment is required to fulfil the diagnosis criteria for dementia. Word recall, such as the Rey Auditory Verbal Learning Test (RAVLT), can distinguish between patients with AD and those without dementia (I). However, an effective encoding of information should be controlled to exclude the influence of depression, anxiety and other emotional states to cognitive problems. Semantic cueing may also help for separating retrieval for storage deficits. For that reason, the Memory Impairment Scale (MIS) (sensitivity of 60% and specificity of 96% for identification of dementia) and the "5 word" test (sensitivity of 91% and specificity of 87% for the identification of AD) are short and simple memory tests that can be useful for a first-line screening tool for medical practitioners. Semantic memory should also be assessed (category fluency test, pictures naming task, word and picture definition), since deficits may be observed in AD and be prominent in Semantic Dementia (SD).

Executive Functions

Executive dysfunctions are observed in several dementia conditions. This impairment results in decreased verbal fluency with speech reduction, verbal stereotypies and echolalia; perseverations of mental set; retrieval deficits; attentional disorders; concrete thinking and in some cases disinhibition, impaired adaptation, and uncontrolled behaviours. These deficits are currently assessed by the Wisconsin card sorting test, the Trail Making test, the Stroop test, the verbal fluency tests, and the digit ordering test which trigger the cognitive processes needed for executive functions. In some dementias, executive dysfunction is only an epiphenomenon, part of a more diffuse and global picture. By contrast, it can be a prominent feature and essential for the diagnosis of other dementias, such as FTD and PSP.

Instrumental Functions

Language (comprehension and expression), reading and writing, praxis (execution and recognition), visuospatial and visuoconstructive abilities can also be more or less affected according to the type of dementia disorder. These cognitive domains, often referred to as instrumental functions, are particularly impaired in diseases with prominent cortical involvement such as AD and DLB and may be the initial domain of dysfunction in lobar atrophy (progressive aphasia syndromes, progressive apraxia, cortico-basal degeneration [CBD] or posterior cortical atrophy).

Cognitive assessment is central to diagnosis and management of dementias and should be performed in all patients (**Level A**). Quantitative neuropsychological testing, ideally performed by someone trained in neuropsychology, should be considered in patients with questionable, prodromal, mild, or moderate dementia (**Level C**). The specialist physician should include a global cognitive measure and in addition more detailed testing of the main cognitive domains including memory, executive functions and instrumental functions (**Level C**).

Assessment of Behavioural and Psychological Symptoms

The accurate identification of behavioural and psychological symptoms of dementia (BPSD) is essential both for diagnosis and management of patients with dementia, but often such symptoms may not be disclosed by patients or caregivers, until they are intolerable or they precipitate a crisis. Earlier detection can be achieved by routine and repeated enquiry. Several rating instruments have been designed for this purpose, enquiring not only about the presence or absence of different symptoms, but also about their frequency, severity and impact upon the caregiver. They usually rely upon the report of an informant who should have regular contact with the patient. Repeated use of such scales can also be useful in monitoring the effects of treatment interventions. Suitable scales include the Neuropsychiatric Inventory (NPI), Behavior Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD) and the Manchester and Oxford Universities Scale for the Psychopathological Assessment of Dementia (MOUSEPAD).

Assessment of behavioural and psychological symptoms of dementia is essential for both diagnosis and management, and should be performed in all patients (**Level A**). Symptoms should be actively enquired about from the patient and a closely involved carer using appropriate rating scales (**Good Practice Point**). Co-morbidity should always be considered as a possible cause (**Level C**).

Assessment of ADL

Assessment of function in daily life is part of diagnostic process and allows clinicians to evaluate the need for personal and institutional care. Different scales are used to objectively measure these abilities. These are based mainly on the interview with the patient and his/her caregiver. Two classical fields measured are basic, or general (such as

eating, dressing, etc.) and instrumental activities (such as the use of devices, shopping). Frequently used scales include the Alzheimer Disease Cooperative Study (ADCS) ADL Scale, Functional Activities Questionnaire (FAQ); the Progressive Deterioration Scale (PDS), and the Disability Assessment for Dementia (DAD).

Impairment of activities of daily living due to cognitive impairment is an essential part of the criteria for dementia and should be assessed in the diagnostic evaluation (**Level A**). A semi-structured interview from the caregiver is the most practical way to obtain relevant information, and a panel of validated scales are available (**Good Practice Point**).

Assessment of Co-morbidity

Co-morbidities are frequent, particularly in elderly patients (**IV**), and may rapidly worsen the cognitive and functional status of the patient. There is a strong association between medical co-morbidity and cognitive status in AD (**IV**), and optimal management of medical illnesses may offer potential to improve cognition. Depression, cardiovascular disease, infections, adverse effects of drugs, delirium, falls, incontinence, and anorexia are frequently observed co-morbidities or complications. Some of the co-morbid conditions which were identified in a large postmortem study of patients with dementia would have affected the clinical management of the patient, had they been known antemortem (**IV**).

Assessment of co-morbidity is important in the evaluation of the patient with dementia, and should be performed not only at the time of diagnosis, but throughout the course of the disease, with particular attention to episodes of sudden worsening of cognitive or behavioural symptoms (**Good Practice Point**).

Blood Tests

Laboratory screening with blood tests is recognized as an important integral part of the general screening of a patient presenting with cognitive disturbances. The aims of blood tests include (1) to identify co-morbidity and/or complications; (2) to reveal potential risk factors; (3) to explore the background of frequently associated confusional states; and (4) more rarely to identify the primary cause of dementia. Cognitive disturbances may be associated with a wide range of metabolic, infectious, and toxic conditions, which should be identified and treated. For most of these conditions, there is no specific evidence from RCTs that treatment will reverse cognitive symptoms. Yet, the specialist physician is often dealing with patients with confusional states, rapid progression or atypical presentation, in whom blood tests may be of diagnostic value.

The following blood tests are generally proposed as mandatory tests for all patients at first evaluation, both as a potential cause of cognitive

	impairment or as co-morbidity: blood sedimentation rate, complete blood cell count, electrolytes, calcium, glucose, renal and liver function tests, and thyroid stimulating hormone. More extensive tests will often be required, e.g., vitamin B12 and serological tests for syphilis, HIV, and Borrelia, in individual cases (**Good Practice Point**).
SIGN (2006)	**Initial Cognitive Testing** The extent to which clinicians assess cognitive function, and their choice of cognitive test, varies widely. The MMSE (see Annex 7 in the original guideline document) was developed as a screening instrument for dementia and is widely used. The brevity of the MMSE results in superficial assessment of memory, language, visuoperceptual function. Processing speed and executive function are not tested. Evidence from a systematic review has shown that the MMSE is suitable for the detection of dementia in individuals with suspected cognitive impairment. The ACE (see Annex 7 in the original guideline document) is a more comprehensive measure of cognitive function that incorporates the MMSE. It is a 100-point test battery assessing six cognitive domains. **B** - In individuals with suspected cognitive impairment, the MMSE should be used in the diagnosis of dementia. **Good Practice Point**. Initial cognitive testing can be improved by the use of Addenbrooke's Cognitive Examination. The IQCODE (see Annex 8 in the original guideline document) is a short questionnaire filled out by someone who knows the patient and can be an adjunct to direct cognitive testing. **Good Practice Point**. A questionnaire, such as the IQCODE, completed by a relative or friend may be used in the diagnosis of dementia. **Screening for Comorbid Conditions** It is good practice to screen for coexisting medical conditions that are common in older people and for potential causes of dementia at first presentation. Reversible causes of dementia, for example, due to hypothyroidism and vitamin B_{12} deficiency are very rare (less than 1%) and very few cases of reversible or partially reversible dementia have been detected by batteries of routine physical investigations. There is no evidence that routine batteries of laboratory tests improve the accuracy of the clinical diagnosis of dementia, nor is there evidence

for the routine use of genetic markers or syphilis serology to increase the predictive value of a diagnosis.

Good Practice Point. Physical investigations including laboratory tests should be selected on clinical grounds according to history and clinical circumstances.

B - As part of the assessment for suspected dementia, the presence of comorbid depression should be considered.

Neuropsychological Testing

Assessment of cognition is useful in both the initial and differential diagnosis of dementia. The added value of neuropsychological testing in patients who have previously received simple but comprehensive cognitive testing has not been established.

Several studies have employed neuropsychology primarily to compare people with AD, FTD, DLB, VaD and depression.

It is possible to detect even very early AD using neuropsychological testing. Neuropsychology is superior to imaging in discriminating people with AD from controls.

Neuropsychological testing also aids in the differential diagnosis of dementia:

- FTD is characterised by deficits of semantic memory and attention/executive function rather than the episodic memory deficit seen in AD
- DLB has more pronounced visuoperceptual and frontal impairment compared to AD
- Vascular dementia exhibits executive dysfunction
- Depression shows a subcortical pattern of cognitive impairment

B - Neuropsychological testing should be used in the diagnosis of dementia, especially in patients where dementia is not clinically obvious.

Good Practice Point. It may be useful to repeat neuropsychological testing after six to 12 months in patients where:

- The diagnosis is unclear
- Measurement of the progression of deficits in a typical pattern supports a diagnosis of dementia and helps in differential diagnosis

Neuroimaging

EFNS (2007)	**Neuroimaging** Structural imaging should be used in the evaluation of every patient suspected of dementia: Non-contrast CT can be used to identify surgically treatable lesions and vascular disease (**Level A**). To increase specificity, MRI (with a protocol including T1, T2 and FLAIR sequences) should be used (**Level A**). SPECT and PET may be useful in those cases where diagnostic uncertainty remains after clinical and structural imaging work up, and should not be used as the only imaging measure (**Level B**).
SIGN (2006)	**The Use of Imaging** **C** - Structural imaging should ideally form part of the diagnostic workup of patients with suspected dementia. **C** - SPECT may be used in combination with CT to aid the differential diagnosis of dementia when the diagnosis is in doubt. The ability of clinical examination (for example, history-taking and physical examination) to predict a structural lesion has been reported as having sensitivity and specificity of 90%. Imaging can be used to detect reversible causes of dementia and to aid in the differential diagnosis of dementia. The choice of imaging technique varies widely, and includes CT, MRI, SPECT and PET. A systematic review showed that clinical prediction rules which attempt to detect those patients who should undergo imaging have poor sensitivity and specificity, and could result in patients with potentially reversible causes of dementia being missed. Measures of medial temporal lobe width on CT can help distinguish dementia from depression, but cannot discriminate between causes of dementia. MRI indices such as hippocampal volumetry can support clinical diagnosis of early AD, assist in differential diagnosis, for example, of VaD, and diagnose sporadic and variant CJD. In one study, MRI was found to be superior to PET and SPECT for aiding diagnosis of dementia, but none is as effective as neuropsychology. Assessment of delayed recall is at least as good as volumetric MRI in distinguishing people with probable AD from controls. A systematic review and several subsequent studies have shown the benefit of SPECT in the diagnosis of AD. While clinical criteria may be more sensitive at detecting AD than SPECT, SPECT provides greater specificity against other types of dementia than clinical criteria. Its use

	in discriminating AD from VaD, DLB and FTD has been demonstrated. Combining structural and functional investigations (for example, CT and SPECT) may lead to a more accurate diagnosis.
CSF and EEG Investigations	
EFNS (2007)	**EEG** The EEG may be a useful adjunct, and should be included in the diagnostic work up of patients suspected of having CJD or transient epileptic amnesia (**Level B**). **CSF** CSF analysis with routine cell count, protein, glucose and protein electrophoresis is recommended in patients with a clinical suspicion of certain diseases and in patients with atypical clinical presentations (**Good Practice Point**). CSF total tau, phospho-tau, and Ab42 can be used as an adjunct in cases of diagnostic doubt (**Level B**). For the identification of CJD in cases with rapidly progressive dementia, assessment of the 14-3-3 protein is recommended (**Level B**).
SIGN (2006)	**The Role of CSF and EEG** **B** - CSF and EEG examinations are not recommended as routine investigations for dementia. **Good Practice Point**. CSF and EEG examinations may be useful where CJD is suspected. Preliminary diagnostic studies have shown that reduced levels of CSF beta-amyloid and increased levels of CSF tau can differentiate patients with AD from patients with other dementias as well as from people without dementia. Although one study reported sensitivity of 92% and specificity of 89% for differentiating between patients with AD and controls using CSF beta-amyloid and tau, there is insufficient evidence to support routine use of CSF markers in the diagnosis of dementia. There is evidence that the presence of 14-3-3 protein in CSF is a predictor for sporadic CJD. One study found 53% sensitivity for diagnosis of CJD by CSF examination, while other studies report sensitivities and specificities of above 90%. There is evidence to support only the limited use of EEG in the diagnosis of dementia, for example, in the diagnosis of sporadic CJD, with reported sensitivity of 65% and specificity of 86%.
Other Investigations	

EFNS (2007)	**Genetic Testing** Screening for known pathogenic mutations can be undertaken in patients with appropriate phenotype or a family history of an autosomal dominant dementia. This should only be undertaken in specialist centres with appropriate counselling of the patient and family caregivers, and with consent (**Good Practice Point**). Pre-symptomatic testing may be performed in adults where there is a clear family history, and when there is a known mutation in an affected individual to ensure that a negative result is clinically significant. It is recommended that the Huntington's disease protocol is followed (**Good Practice Point**). Routine Apo E genotyping is not recommended (**Level B**). **Tissue Biopsy** Tissue biopsy can provide a specific diagnosis some rare dementias. This should only be undertaken in specialist centres in carefully selected cases (**Good Practice Point**).
SIGN (2006)	No recommendations offered

TABLE 4: BENEFITS AND HARMS	
Benefits	
EFNS (2007)	Appropriate diagnosis and management of Alzheimer's disease and other disorders associated with dementia
SIGN (2006)	Implementation of this guideline should: • Improve early identification of dementia • Allow early involvement of professional services in treatment • Ensure that people receive clinically effective treatment at a point where both they and their carers will be able to appreciate the benefits • Ensure that patients and carers have a better understanding of the illness and are able to adjust to difficulties as they arise • Aid management of problems and difficulties, which can delay the need to go into a care home
Harms	
EFNS (2007)	No harms related to diagnosis are provided.

SIGN (2006)	Not stated

TABLE 5: EVIDENCE RATING SCHEMES AND REFERENCES	
EFNS (2007)	**Evidence Classification Scheme for a Diagnostic Measure** **Class I**: A prospective study in a broad spectrum of persons with the suspected condition, using a "gold standard" for case definition, where the test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy **Class II**: A prospective study of a narrow spectrum of persons with the suspected condition, or a well-designed retrospective study of a broad spectrum of persons with an established condition (by "gold standard") compared to a broad spectrum of controls, where test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy **Class III**: Evidence provided by a retrospective study where either persons with the established condition or controls are of a narrow spectrum, and where test is applied in a blinded evaluation **Class IV**: Any design where test is not applied in blinded evaluation OR evidence provided by expert opinion alone or in descriptive case series (without controls) **Evidence Classification Scheme for a Therapeutic Intervention** **Class I**: An adequately powered prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population or an adequately powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations. The following are required: a. Randomization concealment b. Primary outcome(s) is/are clearly defined c. Exclusion/inclusion criteria are clearly defined d. Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias e. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences **Class II**: Prospective matched-group cohort study in a representative population with masked outcome assessment that meets a-e above or

	a randomized, controlled trial in a representative population that lacks one criteria a-e **Class III**: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment **Class IV**: Evidence from uncontrolled studies, case series, case reports, or expert opinion **Rating of Recommendations for a Diagnostic Measure** **Level A rating** (established as useful/predictive or not useful/predictive) requires at least one convincing class I study or at least two consistent, convincing class II studies. **Level B rating** (established as probably useful/predictive or not useful/predictive) requires at least one convincing class II study or overwhelming class III evidence. **Level C rating** (established as possibly useful/predictive or not useful/predictive) requires at least two convincing class III studies. **Rating of Recommendations for a Therapeutic Intervention** **Level A rating** (established as effective, ineffective, or harmful) requires at least one convincing class I study or at least two consistent, convincing class II studies. **Level B rating** (probably effective, ineffective, or harmful) requires at least one convincing class II study or overwhelming class III evidence. **Level C rating** (possibly effective, ineffective, or harmful) requires at least two convincing class III studies. **Good Practice Points** Where there was a lack of evidence but consensus was clear, the Task Force has stated their opinion as good practice points.
SIGN (2006)	**Levels of Evidence** **1++**: High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias **1+**: Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias **1-**: Meta-analyses, systematic reviews of RCTs, or RCTs with a high

risk of bias

2++: High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal

2+: Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal

2-: Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal

3: Non-analytic studies (e.g., case reports, case series)

4: Expert opinion

Grades of Recommendations

Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

Grade A: At least one meta-analysis, systematic review of randomized controlled trials (RCTs), or RCT rated as 1++ and directly applicable to the target population; *or*

A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results

Grade B: A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; *or*

Extrapolated evidence from studies rated as 1++ or 1+

Grade C: A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; *or*

Extrapolated evidence from studies rated as 2++

Grade D: Evidence level 3 or 4; *or*

Extrapolated evidence from studies rated as 2+

Good Practice Points: Recommended best practice based on the

	clinical experience of the guideline development group.

GUIDELINE CONTENT COMPARISON

Areas of Agreement

History Taking and Diagnostic Criteria

EFNS and SIGN agree that a detailed medical history is an important part of the diagnostic assessment and should include the mode of onset, pattern of progression, and cognitive domains affected. There is also agreement that, given that a person with dementia may not be able to give a fully accurate history, the history should be supplemented by an independent informant when possible.

The guidelines agree that the diagnosis of a dementia syndrome can only be made in terms of probability. Both groups agree that the DSM-IIIR/DSM-IV and NINCDS-ADRDA criteria have reasonably good diagnostic accuracy with a sensitivity of approximately 80% for probable AD, and that they are appropriate criteria to use for the diagnosis of probable AD. For the diagnosis of VaD, both groups cite the NINDS-AIREN criteria, with EFNS noting that criteria achieved a low sensitivity (43%), but a good specificity (95%) in the only published class I study. In addition to the NINDS-AIREN criteria, SIGN also recommends the Hachinski Ischaemic Scale. There is agreement that it may be common for patients to present with both AD and vascular pathology, and that mixed pathologies and the prevalent findings of vascular lesions in all patients with dementia add to the complexity of the diagnosis of VaD.

EFNS and SIGN also discuss diagnostic criteria for DLB and FTD. EFNS does not provide specific recommendations, but notes that Consortium for DLB criteria showed rather low sensitivities in class I and II studies. With regard to FTD, they do not address any specific diagnostic criteria, stating that specific sets of pathological findings have not been associated with specific clinical syndromes. According to SIGN, while the clinical criteria for DLB (Consortium for DLB criteria) and FTD (Lund-Manchester criteria) are not closely associated with neuropathological diagnoses, they can still provide useful differentiating clinical features and should be considered in clinical assessment.

Assessment

Both groups agree that cognitive assessment is central to the diagnosis of dementias and should be performed in all patients. Both groups cite the MMSE as an appropriate global cognitive testing tool. SIGN notes that initial cognitive testing can be improved by the use of Addenbrooke's Cognitive Examination, a more comprehensive measure of cognitive function that incorporates the MMSE. The 7-Minute Screen and Clinical Dementia Rating (CDR) tests can be useful for the detection of dementia, according to EFNS. They add that the Mattis Dementia Rating Scale, however, is more appropriate for the assessment and follow-up of FTD and fronto-subcortical dementias. Both groups also agree that informant-

based questionnaires completed by someone who knows the patient, such as the IQCODE, can be useful in the detection of dementia.

Both groups also agree that more advanced neuropsychological testing should also be used in the diagnosis of dementia. According to SIGN, it is possible to detect even very early AD using neuropsychological testing, and it also aids in the differential diagnosis of dementia. EFNS emphasizes that detailed testing of the main cognitive domains including memory, executive functions, and instrumental functions should be performed. To assess memory function, EFNS cites the Rey Auditory Verbal Learning Test (RAVLT), the Memory Impairment Scale (MIS), and the "5-Word" test. The Wisconsin card sorting test, the Trail Making test, the Stroop test, verbal fluency tests, and the digit ordering test are currently used to assess executive function deficits, according to EFNS.

The groups agree that the presence of behavioral and psychological symptoms of dementia (e.g., hallucinations, delusions, behavioral disturbances) must be assessed for. EFNS notes that several informant-based instruments have been designed for this purpose. Suitable scales cited by EFNS include the Neuropsychiatric Inventory (NPI), Behavior Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD) and the Manchester and Oxford Universities Scale for the Psychopathological Assessment of Dementia (MOUSEPAD).

The groups agree that assessment of co-morbidity is important in the evaluation of patients with suspected dementia. Depression is cited by both groups as a comorbidity that should be screened for. EFNS also notes that cardiovascular disease, infections, adverse effects of drugs, delirium, falls, incontinence, and anorexia are frequently observed co-morbidities or complications. Refer to Areas of Differences for additional information.

Neuroimaging

EFNS and SIGN agree that imaging can be used to detect reversible causes of dementia and to aid in the differential diagnosis of dementia. They further agree that structural imaging tests (e.g., CT, MRI) should be routinely used in the diagnostic evaluation of patients with suspected dementia. There is also agreement that functional imaging tests (e.g., SPECT, PET) can be useful in conjunction with functional imaging tests in cases where there is diagnostic uncertainty.

CSF and EEG Investigations

Neither group recommends routine use of CSF or EEG investigations in the diagnosis of dementia. The groups agree, however, that CSF (specifically assessment of the 14-3-3 protein) and EEG investigations can be useful where CJD is suspected. EFNS also recommends CSF analysis with routine cell count, protein, glucose and protein electrophoresis in patients with a clinical suspicion of certain diseases and in patients with atypical clinical presentations. They add that CSF total tau, phospho-tau and Ab42 can be used as an adjunct in cases of diagnostic doubt.

Areas of Differences

Assessment

According to SIGN, reversible causes of dementia are very rare and very few cases of reversible or partially reversible dementia have been detected by batteries of routine physical investigations. They add that there is no evidence that routine batteries of laboratory tests improve the accuracy of the clinical diagnosis of dementia. SIGN therefore recommends that physical investigations including laboratory tests should be selected on clinical grounds according to history and clinical circumstances.

In contrast to SIGN, EFNS states that the following blood tests are generally proposed as mandatory tests for all patients at first evaluation, both as a potential cause of cognitive impairment or as co-morbidity: blood sedimentation rate, complete blood cell count, electrolytes, calcium, glucose, renal and liver function tests, and thyroid stimulating hormone. They add that more extensive tests will often be required, e.g. vitamin B12 and serological tests for syphilis, HIV, and Borrelia, in individual cases.

Other Investigations

Only EFNS provides recommendations for other investigations: genetic testing and tissue biopsy. With regard to genetic testing, they note that screening for known pathogenic mutations can be undertaken in patients with appropriate phenotype or a family history of an autosomal dominant dementia. They add that pre-symptomatic testing may be performed in adults where there is a clear family history, and when there is a known mutation in an affected individual to ensure that a negative result is clinically significant. With regard to tissue biopsy, EFNS states that it can provide a specific diagnosis in some rare dementias. They note that both types of investigations should only be undertaken in specialist centres.

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